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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/700,922	11/03/2003	Johanna Bergmann	830006-2000	5900

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FROMMER LAWRENCE & HAUG
745 FIFTH AVENUE- 10TH FL.
NEW YORK, NY 10151

EXAMINER	
EMCH, GREGORY S	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 12/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/700,922	BERGMANN ET AL.	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Claim 8 has been amended as requested in the amendment filed on 16 October 2006. Following the amendment, claims 8 and 9 are pending in the instant application.

Claims 8 and 9 are under examination in the instant office action.

The Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8 and 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are to directed a method of passive vaccination to prevent and stop

initiation and progression, respectively, of Alzheimer's disease and other associated diseases, wherein the vaccine includes human antibodies or fragments of human antibodies against SEQ ID NO: 2, SEQ ID NO: 6 or SEQ ID NO: 15 and wherein the vaccination comprises administering to a patient in need of vaccination an effective amount of the human antibodies or fragments of human antibodies, thereby vaccinating the patient against Alzheimer's disease and other associated diseases.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, there is no structural or functional limitation to the fragments of the antibodies to SEQ ID NOs: 2, 6 and 15. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the full length antibodies to SEQ ID NOs: 2, 6 and 15 or binding fragments thereof, the skilled artisan cannot envision the detailed chemical structure and/or function of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated full-length antibodies to SEQ ID NOs: 2, 6 and 15 or fragments thereof that bind the proteins of SEQ ID NOs: 2, 6 and 15, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicants are reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 8 and 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The claims are to directed a method of passive vaccination to prevent and stop initiation and progression, respectively, of Alzheimer's disease and other associated diseases, wherein the vaccine includes human antibodies or fragments of human antibodies against SEQ ID NO: 2, SEQ ID NO: 6 or SEQ ID NO: 15 and wherein the vaccination comprises administering to a patient in need of vaccination an effective amount of the human antibodies or fragments of human antibodies, thereby vaccinating the patient against Alzheimer's disease and other associated diseases. The words "prevent" and "stop" as recited in the claims are interpreted as absolutes. In other words, "prevent" is NOT interpreted as "decrease the incidence of" and "stop" is NOT interpreted as "slow" or "inhibit."

The specification at pp.16-25 discloses the isolation of the genes: alzas, alzas1 and alzas2 and the proteins encoded by said genes. At p.22, lines 20-25, it is taught that western blotting was performed on aliquots of protein from both normal and AD

human brain tissue. Here, immunopositive reactions with the ALZab3 antibody were found in both normal and AD brain proteins, but the reaction of the AD proteins was considerably greater. At p.24, lines 1-2, it is taught that no alzas2 cDNA could be amplified from AD lymphocytes or AD brain tissue. Also, at p. 24, lines 11-23, it is disclosed that sera from a patient with sporadic AD and from a patient with the Swedish mutation were subjected to SDS-free PAGE and western blotting. Here, immunoreactions with anti-ALZAS were positive in both samples. At p.26-27, Applicants' provide prophetic examples of therapeutic uses of antibodies of the invention.

Accordingly, the specification is insufficient to enable one skilled in the art to practice the invention as claimed without undue experimentation. No actual therapeutic data is disclosed in the specification from human patients or from an art-accepted animal model for AD or associated diseases. In addition, the expression data presented in the specification is correlative only. Just because a biological molecule correlates with the presence of a disease does not mean it is a therapeutic target. The molecule may accumulate as a *result* of the disease and thus may not play a *causative* role or a role in disease *progression*. Consequently, Applicants have not established a nexus between said data and a method of passive vaccination to prevent and stop initiation and progression, respectively, of Alzheimer's disease and other associated diseases with antibodies (or fragments thereof) to the proteins of the invention. The fact that the specification teaches expression of a protein

of the invention in AD brain and AD serum does not enable the skilled artisan to prevent or treat AD or any other disease. Furthermore, ALZASp2 is not present in AD samples; thus, it is unclear how an antibody to this molecule would have any use in disease treatment.

Applicants have not shown that antibodies of the invention would lower plaque burden (for example) in an animal model of AD. However, even if this art accepted model system was used in the instant specification, (i.e., mice that are transgenic for PDAPP and exhibit Alzheimer's type over production and build up of β-amyloid within the brain), this system is still not recognized as providing the teachings that are predictive of the results expected for the claims (passive vaccination for prevention and treatment of Alzheimer's disease).

Furthermore, there is no known cure, treatment or preventative measure for Alzheimer's disease and related diseases, as evidenced by Vickers (Drugs Aging. 2002; 19(7): 487-94) who teaches, "Alzheimer's disease (AD) is the leading cause of age-related dementia and is set to markedly increase in incidence with the gradual aging of the populations in both developed and developing nations. Along with most brain diseases and conditions, there is no effective treatment currently available to reverse, slow down or prevent its course."

The specification fails to provide any guidance for successfully therapeutically treating or prophylactically treating human patients with Alzheimer's disease (or any patients for that matter), and since resolution of the various complications in regards to treating Alzheimer's disease with an antibody is not complete, one of skill in the art

would be unable to practice the invention without engaging in undue trial and error experimentation. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to practice the claimed methods without undue experimentation. Additionally, a person skilled in the art would recognize that predicting the efficacy of anti-Aβ in humans in an Alzheimer's disease model as highly problematic (see MPEP §2164.03). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods, such a disclosure would not be considered enabling since the state of the treatment of Alzheimer's diseases and associated disease is highly unpredictable.

Also concerning passive immunization, Goldsby et al. ("Vaccines," Chapter 18 from Immunology, 4th Edition, W.H. Freeman and Co. New York, pp.449-465) teaches that it does not allow for the formation of immunological memory, thus requiring continual dosages if the desired immunity is to be maintained. Thus, the issue of the antigenicity of the antibody administered must be taken into consideration because it can trigger and unwanted and possibly harmful immune response (p. 451).

Furthermore, the art teaches that vaccine development is complex and also requires extensive experimentation. For example, De Groot (Drug Discov Today. 2006 Mar; 11(5-6): 203-9) teaches that immunomics involves searching for the antigens and mapping the epitopes that stimulate an immune response. This is accomplished by isolating proteins from whole cells and then digesting them to find epitopes that stimulate a B-cell or T-cell response or by immunomics tools such as T-cell and B-cell-epitope mapping algorithms. The latter method involves mathematical analyses of the

patterns of amino acids that occur in peptides bound to human leukocyte antigen (HLA) by antigen-presenting cells. De Groot cautions that not all epitope-mapping tools are equivalent and teaches that few B-cell-epitope mapping algorithms are in current use and that only a handful of these tools have been validated *in vitro* or *in vivo* (p.203). De Groot also outlines the substantial experimentation necessary in order to identify potential epitope sequences that even still need to be evaluated *in vitro* or *in vivo* before a potential vaccine can be developed (e.g., Figure 1). Such detailed pre-clinical development is missing from Applicants' disclosure.

In addition, Purcell et al. (J Pept Sci. 2003 May; 9(5): 255-81) teach that vaccine development is complex and is challenged by negative immunogenicity of potential vaccines and thus requires the identification of the unknown physiologically relevant epitopes derived from pathogens, tumors and tissues targeted by aberrant autoimmune responses. This coupled with the extensive polymorphism exhibited by HLA molecules creates a challenge for the incorporation of minimal peptide epitopes into immunotherapeutics and diagnostics. "Thus, a combination of bioinformatics, analytical biochemistry and peptide based validation studies needs to be applied to identify useful lead compounds by subsequent exploitation of peptide chemistry" (pp.259-260). Therefore, given that the antibodies of Applicants' invention could result in negative autoimmune responses, much undue trial and error analysis is required in practicing the claimed method.

Also, even when vaccines show potential through induction of a substantial immune response as defined by the antigen antibody titer, they can lack effectiveness in

the clinical setting (see Hanke, Eur J Immunol. 2006 Apr; 36(4): 806-9). In one example regarding a hepatitis B vaccine, "various multivalent combinations of vaccines with drugs and cytokines are being explored to overcome the non-responsiveness to the prophylactic vaccine and to boost and broaden weak HBV-specific T-cell responses in patients with chronic hepatitis B." Accordingly, although some of these techniques are thought to be promising, the results in early clinical trials have been unimpressive (p.807), thus further supporting the unpredictability of the claimed methods.

In addition, the claimed method encompasses administering anti-DNA molecules (antibodies to SEQ ID NOs: 2 and 15). While the art has implicated a use for anti-DNA antibodies in diagnostics, it is not established that these molecules can be used for therapy. Rather, anti-DNA molecules are implicated in a variety of disease states, including cancer progression and autoimmune disease. Specifically, Kim et al. (Immunology. 2006 Oct; 119 (2): 254-64) teach that DNA-IgG complexes contribute to the pathogenesis in autoimmune disease that leads to persistent inflammation and results in tissue damage. Also, DNA-IgG complexes lead to immunological tolerance and an impaired immune response in cancer, thus leading to tumor progression (see p.260, figure 2). Thus, the therapeutic use of anti-DNA antibodies benefit in any disease state is unpredictable.

As set forth above, inadequate guidance is presented in the specification to overcome the obstacles outlined above in practicing the claimed invention. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. Given the lack of working examples involving

prophylaxis and treatment of any patient with any disease (AD or otherwise), comprising administering an antibody of the invention, it is unpredictable as to which variations, if any, meet the limitations of the claims. Applicants are required to enable one of skill in the art to practice the claimed invention; however, the specification only teaches one skilled in the art to identify genes and proteins of the invention. The specification fails to provide adequate guidance for the skilled artisan to overcome the unpredictability and challenges of applying results from treatment and prophylaxis of Alzheimer's disease in animals to humans as exemplified in the references herein. Therefore, it would require undue experimentation for one of skill in the art to practice the claimed invention.

Claim Rejections - 35 USC § 112, second paragraph

Claims 8 and 9 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that claims 8 and 9 fail(s) to correspond in scope with that which applicant(s) regard as the invention can be found in the **sequence listing dated 14 October 2004** and in the remarks from the reply filed 16 October 2006. In said sequence listing, it is stated that **SEQ ID NOs: 2 and 15 are nucleic acid molecules and are not amino acid molecules.** This statement indicates that the invention is different from what is defined by Applicants in the claim(s) because, according to Applicants, the claims are drawn to a method of passive vaccination to prevent and stop initiation and progression, respectively, of Alzheimer's disease and other associated diseases, wherein the vaccine includes human antibodies or fragments of human antibodies against amino

acid molecules of SEQ ID NOs: 2, 6, or 15. It is noted that although Applicants amended claim 8 by deleting reference to the antibodies being raised against protein fragments, Applicants assert in the remarks from the reply filed 16 October 2006, "To expedite prosecution, claim 8 has been clarified by reciting SEQ ID NOs: **2, 6 and 15**, which are the **amino acid sequences** of the protein fragments of claim 8." Thus, it is unclear what Applicants regard as their invention.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached on Monday through Friday from 9AM to 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached at (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gregory S. Emch, Ph.D.
Patent Examiner
Art Unit 1649
06 December 2006

ELIZABETH KEMMERER
PRIMARY EXAMINER